Cyanotic Congenital Heart Disease

Introduction

Following on the heels of the last lesson, in which we described left-to-right shunts and noncyanotic congenital heart defects, this lesson is about catastrophic anatomical failure and **cyanotic congenital heart defects**. Did you see what we did there? Many sources will educate this subject material as left-to-right shunts (pink baby) versus right-to-left shunts (blue baby), as if cyanotic and noncyanotic imply mirrored pathophysiology. No. There is a condition that is a right-to-left shunt, where deoxygenated blood is pushed across a simple lesion, such as a ventricular septal defect. That was called Eisenmenger syndrome. Cyanotic congenital heart defects, except for tetralogy of Fallot, are universally fatal. Some newborns can be saved with heart surgery the day of birth, and some are born stillborn.

All the cyanotic congenital heart defects begin with a "T"—Tetralogy, Transposition of the great arteries, Truncus arteriosus, Tricuspid atresia, Total anomalous pulmonary venous connection. **All cyanotic conditions are caused by neural crest failure**.

Tetralogy of Fallot

The truncus arteriosus is one common structure in the primitive heart tube that goes on to form both the aorta and the pulmonary artery. The common ventricle is divided by the **muscular interventricular septum** formed by the mesodermal structures of the heart muscle. The truncus arteriosus is divided by the **aorticopulmonary septum**, derived from **ectoderm (neural crest cells)**, splitting the truncus arteriosus into the pulmonary artery and aorta. That same aorticopulmonary septum also completes the septation of the right ventricle from the left ventricle by forming the **membranous interventricular septum** (the same thing that failed to form in a simple VSD in the last lesson). In tetralogy of Fallot (Tetralogy for short), the defect is almost identical to an isolated VSD, but the small variation causes a completely different syndrome. The aorticopulmonary septum forms, and the aorta and pulmonary artery are separated from each other. But the aorticopulmonary septum misses the midline and ends up anterior to where it should be. The truncus arteriosus is one common tube that must be divided into an aorta and a pulmonary artery. It is also the start of the ventricular outflow tract. If the aorticopulmonary septum misses and creates a larger aorta than it should, then whatever is left over of the ventricular outflow tract is for the pulmonary artery. And because it misses the endocardial cushion, its continuation off course anteriorly makes it incapable of completing the interventricular septum.

Too much room for the aorta	Less room for the pulmonary artery	And a gap between the ventricles
(Overriding aorta)	(Pulmonary stenosis)	(Ventricular septal defect)

When the aorticopulmonary septum misses the interventricular septum, it means there is a **ventricular septal defect** immediately at the outflow tract. When the aorticopulmonary septum unevenly divides the truncus arteriosus, it means that the aorta has more space at the common outflow tract, called an **overriding aorta**. If the aorta has more space, then the pulmonary artery must have less space. When a vessel "has less space," it is called stenosis; therefore, this condition causes **pulmonary artery stenosis**. The pulmonary artery is not stenotic like the aortic valve gets with age (calcifications) or rheumatic heart disease (fissure of commissures). Rather, there is less valve area, less pulmonary artery. That means that the right ventricle must contract against a high-resistance aorta or a higher-than-usual-resistance pulmonary artery. And because, as a general principle, a ventricle hypertrophies if it has to push against higher resistance, the right ventricle will **hypertrophy**.

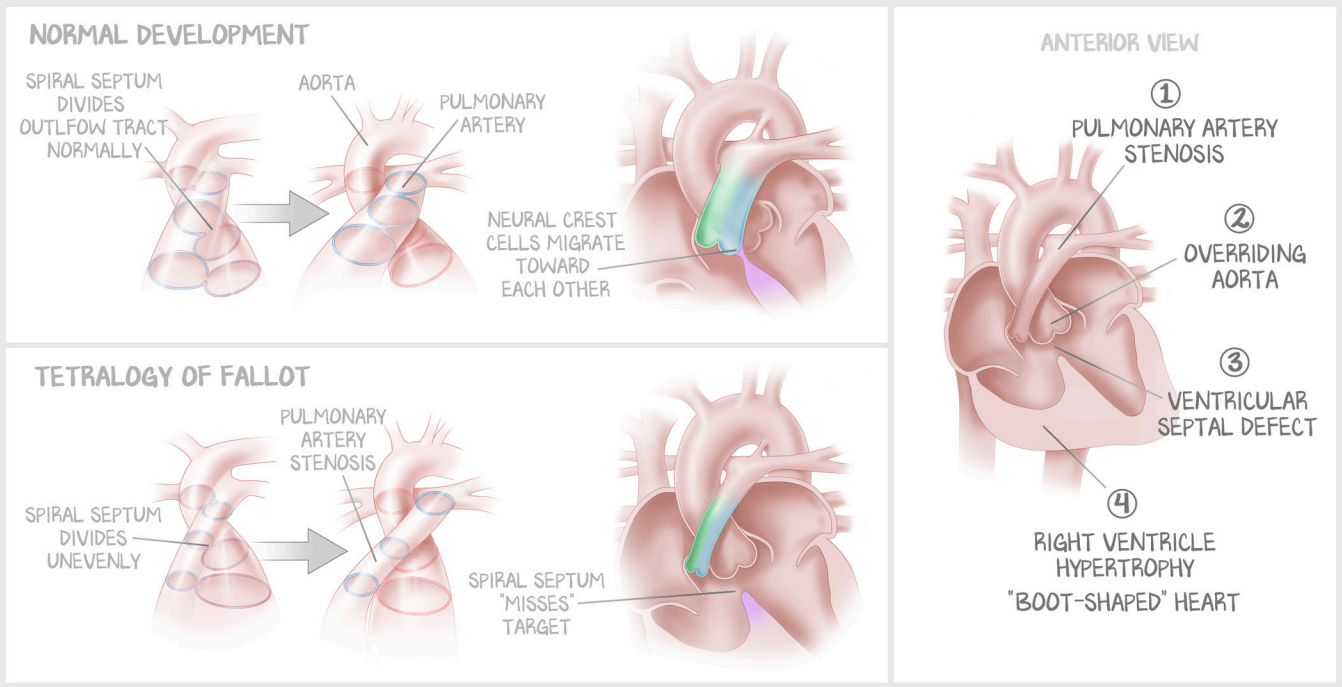

Figure 5.1: Tetralogy of Fallot
The anterior displacement of the aorticopulmonary septum leads to its anatomical arrangement. Notice how the aorta and pulmonary artery have the same radius in the normal development, but the pulmonary artery is much smaller in the Tetralogy illustration. In Tetralogy, there is an overriding aorta, a ventricular septal defect, and, as a result of the overriding aorta, pulmonary stenosis that leads to right heart hypertrophy.

The diagnosis of tetralogy of Fallot can be made at any age. On licensing exams, consider it the cyanotic congenital heart defect of childhood, the only one that can go undiagnosed for longer than a day. Children who have Tetralogy will present with **tet spells**. At baseline, the systemic vascular resistance is higher than the pulmonary vascular resistance, but the pulmonary vascular resistance is much higher than normal. Blood takes the path of least resistance. Before exercise, there is a certain amount of resistance (and therefore flow) through the pulmonary artery and aorta. Then the child exercises, running around and playing. The skeletal muscles in the legs feel the increased demand and instruct their arterioles to bring in more blood (*hyperemia*). The arterioles comply with vasodilation. Because there are many arterioles in skeletal muscle in the legs, and systemic vascular resistance is the combined resistance of all arterioles, massive vasodilation in the skeletal muscle decreases the peripheral vascular resistance. It makes no change to the pulmonary vascular resistance but relatively decreases the systemic vascular resistance. Blood takes the path of least resistance, and so more blood—both oxygenated and deoxygenated—exits through the aorta. The skeletal muscle of the legs don't get what they asked for—although there is more blood flow, more of it is deoxygenated. While exercising without oxygen (anaerobic state), lactic acid builds up, and the legs hurt. The child **squats**. Remember, this happened because of the relative change in systemic vascular resistance. There is no preload effect in this condition (squatting increases preload temporarily, providing minor relief, but the pain continues). Instead, **sustained squatting** for minutes after exercise mechanically clamps down on those skeletal muscle vessels, increasing systemic vascular resistance. The prolonged increase in systemic vascular resistance restores the balance—the systemic vascular resistance increases enough to get more blood flowing into the pulmonary artery. Children may develop right ventricular hypertrophy, classically tested as having a **boot-shaped heart.** If late in their disease, they will exhibit Eisenmenger syndrome—clubbing and cyanosis—in addition to tet spells.

Transposition of the Great Arteries

If the neural crest cells of the aorticopulmonary septum failed to complete their descent to the myocardial ventricular septum, we get an isolated ventricular septal defect (VSD). If the neural crest cells of the aorticopulmonary septum failed to complete their descent and ended up a little anterior to where they should have, we get Tetralogy. If the **neural crest cells** of the aorticopulmonary septum complete their journey to the endocardial cushion **but fail to twist**, we get **transposition of the great arteries** (TGA)—the aorta is connected to the right ventricle, and the pulmonary artery is connected to the left ventricle.

This effectively creates two circulations: (1) left atrium–left ventricle–lungs–pulmonary vein–left atrium, and (2) right atrium–right ventricle–systemic vasculature–vena cava–right atrium. The left side pumps and receives oxygenated blood to and from the lungs. The right side pumps and receives deoxygenated blood to and from the periphery. In utero, the oxygenated blood is coming from the umbilicus, and the pulmonary vascular resistance is high, so a fetus with TGA can develop normally. But as soon as baby is delivered, there is no way to oxygenate any of the blood going to or coming from the periphery. Without any connection between the two systems, this disease is **incompatible with life**. The two systems were connected by the ductus arteriosum. Before the ductus closes after birth, the two systems are still connected by the ductus arteriosum.

TGA is associated with **pre-existing, poorly controlled maternal diabetes** at the time of conception (it must be pre-conception diabetes and not gestational diabetes because the heart forms between week 3 and week 8, whereas gestational diabetes does not start until week 20). At the time of birth, the hallmark signs of this condition is cyanosis, and blood oxygen saturation **fails to improve after administering supplemental oxygen**.

In order to survive until life-saving surgery, the ductus arteriosus, the only connection between the oxygenated circulation and the deoxygenated circulation, must remain open. At first, oxygenated blood from the pulmonary circuit continues to flow through the ductus into the deoxygenated systemic circuit. Baby can remain oxygenated through the ductus. But a high oxygen tension is being pushed through the ductus arteriosus. That is THE signal for endothelial cells to turn off prostaglandin production, for the myofibroblasts of the tunica media to proliferate, close off the ductus, and scar. The process of fully closing the ductus takes **several days**. If the ductus isn't kept open, a normal-appearing child on the day of birth will suddenly **become cyanotic around day 3 of life**. In truth, the more likely presentation is a bluish baby at delivery who gets worse as the days progress. Intravenous infusion of **prostaglandin E** (Eeeee to keeeep the ductus open) prevents that from happening.

Of course, another septal defect, such as a VSD or ASD, can support life as well. There is no physiological mechanism to close them off. These are the babies with TGA that appear normal at delivery. Large defects allow for partial mixing of the blood. No defect will keep the baby alive for long after birth. TGA requires urgent surgery to fix. If there is another defect, it can be corrected simultaneously.

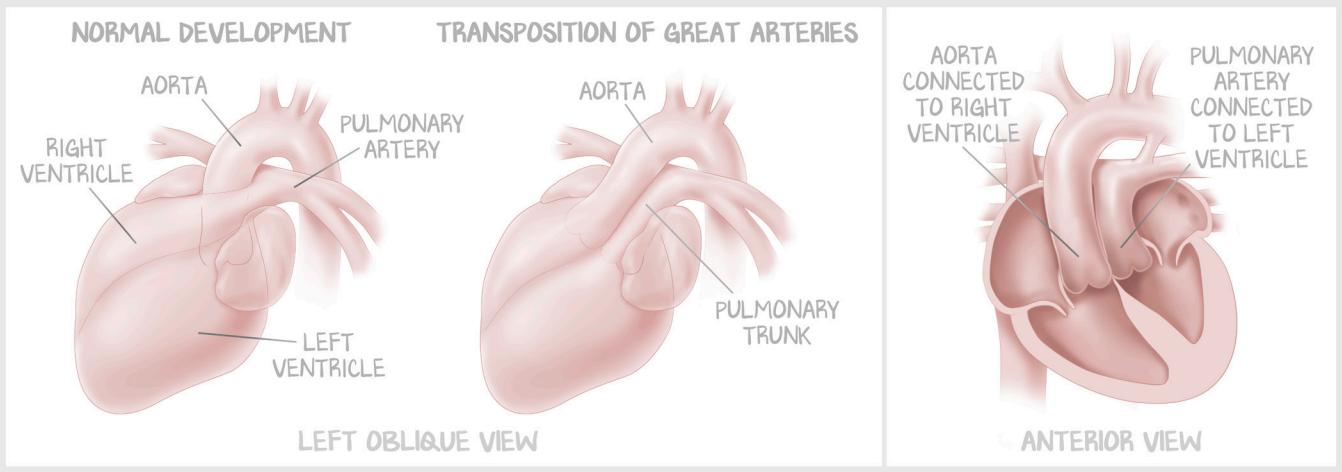

Figure 5.2: Transposition of the Great Arteries
In normal development, the aorta and pulmonary artery originate as one common tube, then are split into two spiraling tubes, the aorta connected to the left ventricle on the right side of the heart, the pulmonary artery connected to the right ventricle on the left side of the heart. In transposition of the great arteries, the aorticopulmonary septum forms but fails to twist, leaving the great arteries connected to the wrong ventricles and connected to each other by the ductus arteriosus.

The process by which the right and left ventricles develop is the complete opposite of the normal process. Because the right ventricle is connected to the high-pressure aorta throughout all of development, the **right ventricle hypertrophies**. Because the left ventricle is connected to the pulmonary circuit, it develops as if it were the right ventricle and is not as hypertrophied. Be careful with the language. Because the foramen ovale is open, the left atrium and left ventricle still get plenty of volume, so they are **not hypoplastic**. Nor do they see the resistance of the aorta, so they are **not hypertrophied**.

Persistent Truncus Arteriosus

When the neural crest cells of the aorticopulmonary septum didn't complete their journey to the endocardial cushion, a VSD was created. When the neural crest cells of the aorticopulmonary septum missed anteriorly, they caused the VSD that came along with the overriding aorta and pulmonary stenosis of Tetralogy. When the neural crest cells of the aorticopulmonary septum formed the septum correctly but forgot to twist, transposition of the great arteries happened. When the neural crest cells of the aorticopulmonary septum fail to do anything at all, that is, the **aorticopulmonary septum fails to form**, you get **truncus arteriosus** (PTA).

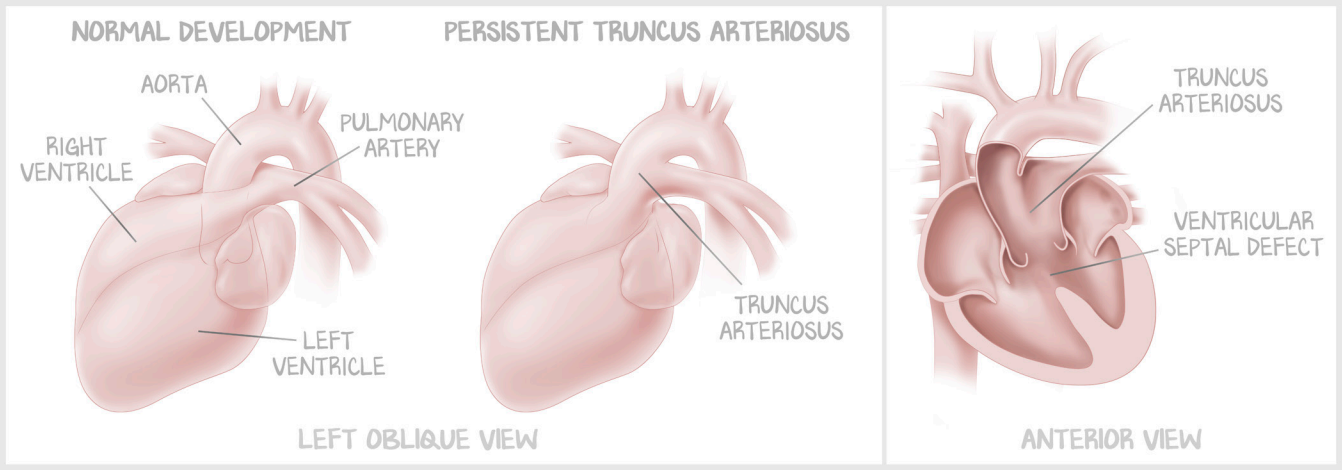

Figure 5.3: Persistent Truncus Arteriosus
In normal development, the aorta and pulmonary artery form from a common truncus arteriosus, separated by the aorticopulmonary septum. If the aorticopulmonary septum fails to form, there will be no membranous interventricular septum (a VSD), one common ventricular outflow tract, one common valve, and one common trunk connecting both the right and left ventricles to both the aorta and pulmonary artery. Neonates can survive with emergency surgery, but most cases are stillborn or fatal.

This common connection means there will be mixing of right ventricle blood with left ventricle blood, which means that **partially oxygenated blood** is sent to both the **aorta** AND the **pulmonary artery**. Remember that blood follows the path of least resistance, and the left ventricle provides a lot of force. This means that not only will partially oxygenated blood leave through the aorta, but the **volume delivered to the pulmonary artery** will be substantially increased (because the pulmonary artery has a much lower resistance). The high volume to the pulmonary artery after birth would eventually cause pulmonary hypertension; however, the mixing of right ventricle blood with left ventricle blood produces such profound systemic hypoxemia that unless this condition is corrected surgically, the patient dies.

Tricuspid Atresia

You may have noticed that we have been progressing through this lesson with progressively worse anatomical failures and even worse outcomes. **Tricuspid atresia** has nothing to do with the truncus or aorticopulmonary septum, but it does still involve **neural crest migration**. Neural crest cells form the atrioventricular septum as the endocardial cushion. If they fail to form a gap for the tricuspid valve, the developing right ventricle will not receive any volume. If a ventricle fails to receive any blood volume, it has nothing to contract against. A **developing heart must have blood to pump in order to develop**. In true, isolated tricuspid atresia, there is no way for the right ventricle to receive blood, so there is a **hypoplastic ventricle**. This is extremely rare. The pregnancy can be brought to term because the right atrium passes blood to the left atrium, and the lung is bypassed; however, most fetuses die in utero because the oxygenated-to-brain and deoxygenated-to-umbilical arteries arrangement is lost. If hypoplastic, the **chamber will never develop**. In isolation, the finding is fatal.

If there were multiple anatomical defects, such as both ASD and VSD and tricuspid atresia, it is theoretically possible to develop the right ventricle. However, we passed the line of esoterism at the last paragraph's "fatal."

Total Anomalosomething or Whatever

Do not learn this. Netter drew a picture of it once. CIBA talks about it. Do not learn this unless you become a pediatric cardiothoracic heart transplant surgeon.

There are many other congenital abnormalities. Learn only Tetralogy, Transposition, and Truncus for the cyanotic congenital defects.

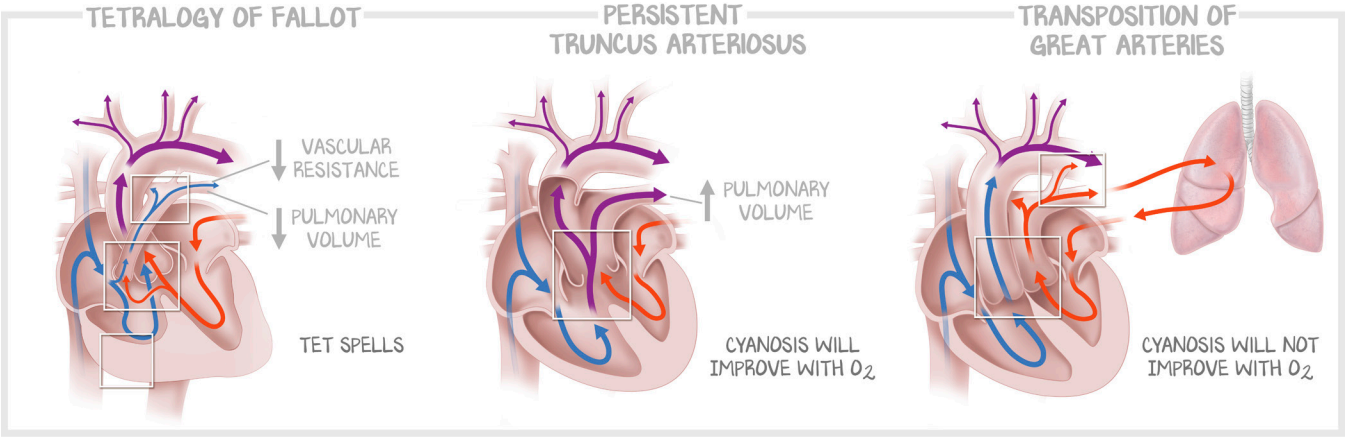

Figure 5.4: Schematic of Cyanotic Heart Disease
In tetralogy of Fallot, there is an overriding aorta, pulmonic stenosis, and ventricular septal defect. The outcome is right ventricular hypertrophy that can reverse to form Eisenmenger's. Before that happens, the children will present with Tet spells. In persistent truncus arteriosus, there is one common outflow tract, one common great artery. The lungs are working and are connected by a ventral septal defect and to both ventricles. The baby is born blue and the cyanosis will improve with oxygen. In transposition of the great arteries , there are two independent circuits. One sends oxygenated blood to the lungs to get more oxygenated. The other send deoxygenated blood to the tissue where oxygen is used. Without a patent ductus, the patient dies.

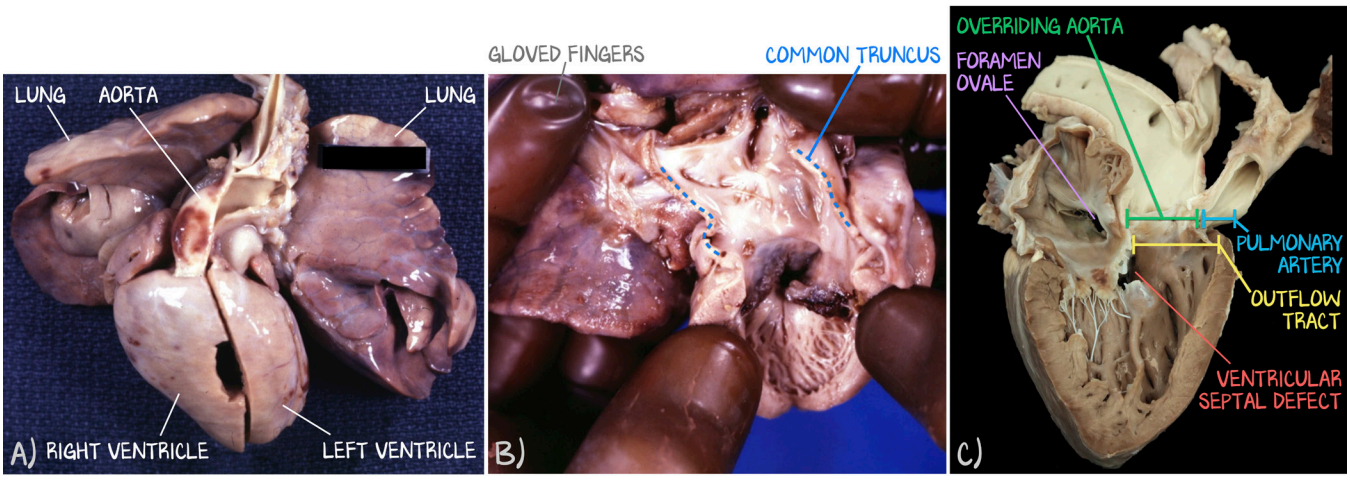

Figure 5.5: Examples of Cyanotic Defects
(a) Gross anatomy of a stillborn. The right ventricle is connected to the aortic arch, demonstrating transposition. The lungs are present for orientation. (b) Notice how small this heart is (the pathologist's brown gloved fingers for reference. There is one outflow tract connected to one large blood vessel. This is truncus arteriosus (c) Seen from the left ventricle with the anterior cut away, you can see that the aorta has nearly double the width of the outflow tract than the pulmonary artery. This is Tetralogy—overriding aorta, pulmonary stenosis, and a membranous ventricular septal defect."